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Pd/C-Catalyzed Chemoselective Hydrogenation in the Presence of Diphenylsulfide

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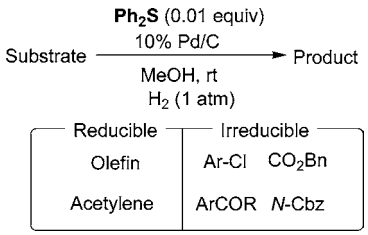
ABSTRACT



A Pd/C-catalyzed chemoselective hydrogenation using diphenylsulfide as a catalyst poison has been developed. This methodology selectively hydrogenates olefin and acetylene functionalities without hydrogenolysis of aromatic carbonyls and halogens, benzyl esters, and *N*-Cbz protective groups.

Transition-metal-catalyzed hydrogenation methods have been applied to a number of chemical transformations of functional groups.[1] Chemoselective hydrogenation among some reducible functionalities has been one of the most important subjects in the field of synthetic chemistry. Catalytic hydrogenations are usually suppressed or degraded by catalyst poisons, such as sulfur or nitrogen-containing molecules.[1,2] Several applications of catalyst poisons have been studied to develop a chemoselective hydrogenation method; such methods usually lack generality except for a few examples, such as the Lindlar catalyst[3] and Rosenmund's reduction.[4] Although Pd/C is known as the most universal catalyst for hydrogenation, it has poor selectivity due to its efficient catalytic activity.[1] Recently, we have reported that the addition of a nitrogen-containing base to a Pd/C-catalyzed hydrogenation system selectively suppressed the hydrogenolysis of benzyl ether in the presence of other reducible functionalities, such as olefin, benzyl ester, and so on.[5,6] However, aromatic *N*-Cbz (benzyloxycarbonyl) and aromatic halogen functionalities are hydrogenated under those reaction conditions.[5] During our efforts to solve the problem, we found that the addition of a sulfur-atom-containing catalyst

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001. (c) Hudlickey, M. *Reductions in Organic Chemistry*, 2nd ed.; American Chemical Society: Washington, DC, 1996. (d) Rylander, P. N. *Hydrogenation Methods*; Academic: New York, 1985.

(2) (a) Baltzly, R. *J. Am. Chem. Soc.* **1952**, *74*, 4586. (b) Horner, L.; Reuter, H.; Herrmann, E. *Justus Liebigs Ann. Chem.* **1962**, *660*, 1. (c) Baltzly, R. *J. Org. Chem.* **1976**, *41*, 928.

(3) Lindlar, H.; Dubuis, R. *Organic Syntheses*; John Wiley & Sons: New York, 1973; Collect. Vol. 5, p 880.

(4) (a) Rosenmund, K. W. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 585. (b) Rosenmund, K. W.; Zetzsche, F. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 425. (c) Mosettig, E.; Mozingo, R. *Org. React.* **1948**, *4*, 362. (d) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1958**, *80*, 5377.

(5) (a) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465. (b) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1997**, *38*, 399. (c) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedon Lett.* **1998**, *39*, 7127. (d) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981. (e) Sajiki, H. *Yakugaku Zasshi* **2000**, *120*, 1091. (f) Sajiki, H.; Hirota, K. *Chem. Pharm. Bull.* **2003**, *51*, 320.

(6) (a) Sajiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990. (b) Sajiki, H.; Hattori, K.; Hirota, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4043. (c) Sajiki, H.; Hattori, K.; Hirota, K. *Chem. Commun.* **1999**, 1041. (d) Sajiki, H.; Hattori, K.; Hirota, K. *Chem.—Eur. J.* **2000**, *6*, 2200. (e) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2000**, *56*, 8433. (f) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 4817. (g) Sajiki, H.; Hirota, K. *J. Org. Synth. Chem. Jpn.* **2001**, *59*, 109.

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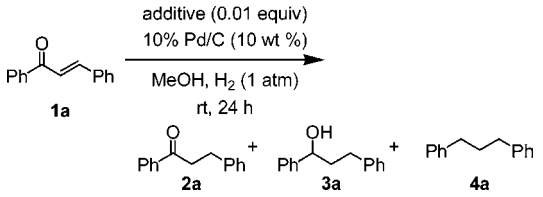
poison controls the catalytic activity of Pd/C with a difference in the suppressive effect from that of a nitrogen-containing base. Herein, we describe the Pd/C-catalyzed chemoselective hydrogenation using diphenylsulfide as a sulfur-containing catalyst poison for the first time.

It is well-known that aromatic carbonyls are easily reduced to form methylene compounds via benzyl alcohol as an intermediate under Pd/C-catalyzed hydrogenation conditions,[1] and it is difficult to achieve the selective hydrogenation of an olefin while leaving the aromatic carbonyl group intact. We have reported a chemoselective partial hydrogenation method of aromatic carbonyls to form benzyl alcohols without hydrogenolysis of the intermediary benzyl alcohol using Pd/C(en) as a catalyst.[6b,f] Therefore, we first attempted the chemoselective hydrogenation of olefin functionality without any reduction of the aromatic ketone.

In the beginning, we attempted a Pd/C-catalyzed reduction of chalcone (**1a**) in the presence of various sorts of sulfur-containing compounds at ordinary pressure and temperature. Upon the use of commercial 10% Pd/C (Aldrich, 205699) in the absence of an additive, the hydrogenation of the olefin and aromatic ketone readily proceeded to give fully hydrogenated 1,3-diphenylpropane (**4a**) quantitatively (Table 1, entry 1). The addition of 0.01 equiv of diphenylsulfone and diphenylsulfoxide could not depress the hydrogenation of aromatic ketone (entries 2 and 3). However, diphenyldisulfide and thiophenol, which are very strong catalyst poisons, completely deactivated 10% Pd/C and only afforded the starting material (**1a**) (entries 7 and 8). On the other hand, we found that the addition of diphenylsulfide completely blocked hydrogenation of only the aromatic ketone, while hydrogenation of the olefin proceeded smoothly and chemoselectively.[7] Reduction of the diphenylsulfide to 0.001 equiv did not exert sufficient suppressing effect on the Pd/C-catalyzed hydrogenation of aromatic ketone (entry 4).

Table 1. Optimization of the Reaction Conditions

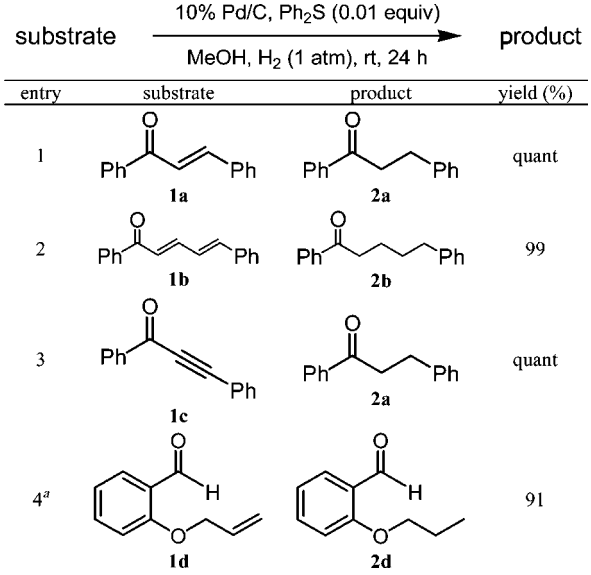


entry	additive	**1a**:**2a**:**3a**:**4a**[a]
1	none	0:0:0:100
2	Ph_2SO_2	0:0:100:0
3	Ph_2SO	0:93:7:0
4	Ph_2S (0.001 equiv)	0:94:6:0
5	**Ph_2S**	**0:100:0:0**
6	Ph_2S (0.1 equiv)	0:100:0:0
7	Ph_2S_2	100:0:0:0
8	PhSH	100:0:0:0

[a] The ratio was determined based on ^{1}H NMR analysis. It contains the error limit of ±5%.

To explore the generality of the effect of diphenylsulfide as an additive toward the selective hydrogenation between aromatic carbonyls and C−C multiple bonds, some substrates possessing different functionalities within the molecule were investigated (Table 2). Selective hydrogenation of multiple bonds in the presence of an aromatic ketone was achieved under our conditions (entries 1−3). Although partial hydrogenolysis of an aromatic aldehyde proceeded in MeOH, complete suppression of the hydrogenolysis of an aromatic aldehyde was achieved in AcOEt (entry 4).[8]

Table 2. Application to the Aromatic Carbonyl Group



[a] The reaction was performed in AcOEt.

Next, we examined the selective hydrogenation between aromatic halogen and olefin functionalities (Table 3). No hydrogenation of aromatic chlorides was observed under the conditions (entries 1−5).[9] The hydrogenolysis of aromatic bromides was also depressed by the addition of 0.5 equiv of diphenylsulfide (entries 6 and 7).

While benzyl ester and *N*-Cbz protective groups are widely used in organic synthesis and can be removed by mild catalytic hydrogenolysis using Pd/C as a catalyst,[10] it is extremely difficult to achieve selective hydrogenation of

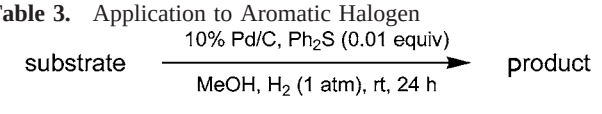
(7) **Typical Procedure for the Chemoselective Hydrogenation of Olefins in the Presence of Ph_2S as a Catalyst Poison**: After two vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the mixture of the substrate (0.500 mmol), 10% Pd/C (10 wt % of the substrate), and diphenylsulfide (0.84 μL, 5.00 μmol) in MeOH (2 mL) was vigorously stirred at room temperature (ca. 20 °C) under 1 atm of hydrogen for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex-LH, 0.45 μm), and the filtrate was concentrated to provide the product.

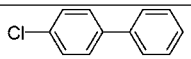
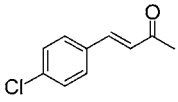
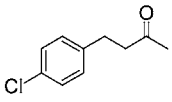
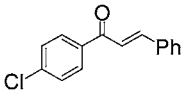
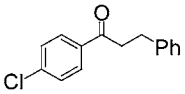
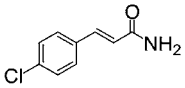
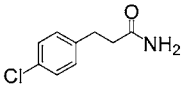
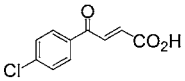
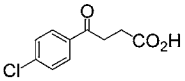
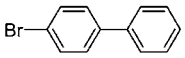
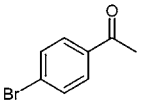
(8) (a) Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654. (b) Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901.

(9) The hydrodehalogenation smoothly proceeded in the absence of Ph_2S. See: (a) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, *43*, 7247. (b) Sajiki, H.; Kume, A.; Hattori, K.; Nagase, H.; Hirota, K. *Tetrahedron Lett.* **2002**, *43*, 7251.

(10) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

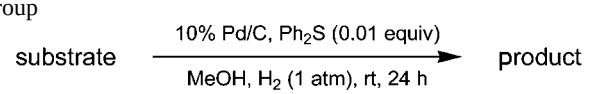
Table 3. Application to Aromatic Halogen

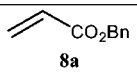
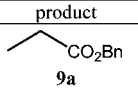
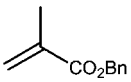
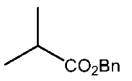
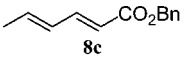
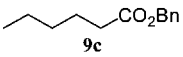
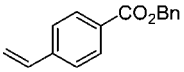
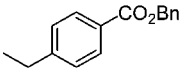
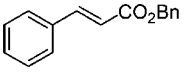
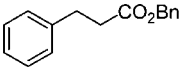
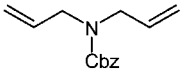
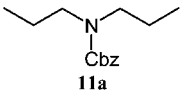
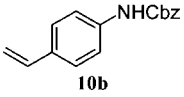
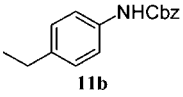
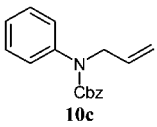
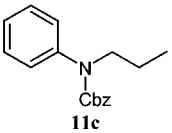


entry	substrate	product	yield (%)
1	 **5a**	no reaction[9]	-
2	 **5b**	 **6b**	98
3	 **5c**	 **6c**	97
4	 **5d**	 **6d**	90[a]
5	 **5e**	 **6e**	99
6[b]	 **7a**	no reaction[9]	-
7[b]	 **7b**	no reaction	-

[a] The yield was determined based on ^{1}H NMR analysis; 10% of the starting material (**5d**) remained. [b] Diphenylsulfide (0.5 equiv) was added to the reaction mixture.

Table 4. Application to Benzyl Ester and *N*-Cbz Protective Group



entry	substrate	product	yield (%)
1	 **8a**	 **9a**	100[a]
2	 **8b**	 **9b**	100[a]
3	 **8c**	 **9c**	quant
4	 **8d**	 **9d**	95
5	 **8e**	 **9e**	94
6	 **10a**	 **11a**	quant
7	 **10b**	 **11b**	98
8	 **10c**	 **11c**	99

[a] The yield was determined based on ^{1}H NMR analysis. It contains the error limit of ±5%.

olefins in the presence of such protective groups. Misiti et al. have reported 3% Pd/C-catalyzed selective hydrogenation of the olefin of γ-amino-α,β-unsaturated (conjugated) esters in the presence of a benzyl ester or an *N*-Cbz protective group.[11] However, the method does not have sufficient generality, and careful monitoring of the reaction is necessary because time-dependent hydrogenolysis of the protective groups was observed. Hence, we investigated the effect of diphenylsulfide as an additive toward the Pd/C-catalyzed hydrogenolysis of benzyl ester and *N*-Cbz protective groups (Table 4). The corresponding olefins of substrates were selectively hydrogenated in the presence of a benzyl ester or an *N*-Cbz protective group[12] (entries 1−5).

In conclusion, we have developed a Pd/C-catalyzed chemoselective hydrogenation method between olefin (acetylene) and other reducible functionalities, such as aromatic carbonyls and halides, benzyl esters, and *N*-Cbz protective groups in the presence of diphenylsulfide as an additive under mild reaction conditions. Therefore, the method is promising as a general and practical chemoselective hydrogenation process in synthetic organic chemistry. Preliminary experiments indicated that the present method can be applied to some aliphatic unsaturated ketones, and the results will be published in the near future.

Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Misiti, D.; Zappia, G.; Monach, G. D. *Synthesis* **1999**, 873.

(12) We have recently reported the similar chemoselective hydrogenation method has been achieved by the use of Pd/Fib catalyst, while a feature of the hydrogenation of benzyl esters and *N*-Cbz protective groups was strongly influenced by the solvent. See: (a) Sajiki, H.; Ikawa, T.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 8437. (b) Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 2217.